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Antibiotics and Chemotherapy

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IN THE HISTORY of man's struggle against infectious diseases and epidemics, certain great discoveries stand out. By far the most important of these was the recognition of the fact that bacteria, protozoa, viruses, and other microscopic forms of life are the agents responsible for causing infectious diseases.

The ancients designated as pests, plagues, or pestilences those diseases which were epidemic in nature. They frequently ascribed such epidemics to the wrath of the gods. A study of the Bible convinces one of the early remarkable understanding of the infectious nature of diseases, methods of prevention, and even of treatment. Deuteronomy alone abounds in such illustrations. In Chapter XXIII, this passage: "And a place shalt thou have without the camp, whither thou shalt go forth abroad: And a spade shalt thou have with thy weapons; and it shall be, when thou sittest abroad, that thou shalt dig therewith, and shalt afterward cover that which cometh from thee." In Chapter XXIV: "Take heed of the plague of leprosy, to observe diligently, and to do according to all that the priests, the Levites, may instruct you; as I have commanded them, so shall ye observe to do." And in Chapter XXVIII: "The Lord will cause the pestilence to cleave unto thee, until it have consumed thee from off the land, whither thou goest to possess it. The Lord will smite thee with consumption, and with fever, and with inflammation, and with extreme burning."

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Gradually it became recognized that such diseases are caused by living organisms, which are transmitted directly or indirectly from the diseased to the healthy. The final recognition of the microbial origin of disease came during the latter part of last century.

Louis Pasteur stands out as the central figure in establishing the fact that bacteria and different other microbes are largely responsible for the causation of infectious diseases. Although he himself did not isolate many of the infectious agents, he established the significance of infection, immunization, and vaccine therapy, the three broad principles that dominated the recognition of nature and treatment of infectious diseases before the recent advent of chemotherapy. He contributed, incidentally, in large measure, to the domestication of microbial forms of life. Pasteur's work led to a tremendous upsurge of efforts to correlate the occurrence and distribution of bacteria and other microorganisms with the causation of specific diseases. Experimental procedures were devised for studying the nature of the disease-producing agents and for the preparation of various biological and chemical agents for the control of infectious diseases.

Robert Koch is the other great pioneer in the field of discovery of causation of disease and methods of treatment. His study of the life cycles of bacteria and his methods for the isolation, cultivation, and staining of bacterial agents served further to advance the science of microbiology and led him to the discovery, in 1882, of the tubercle bacillus, and thus to establishment of the infectious nature of tuberculosis. Although his other great discovery, tuberculin,

which he thought would serve as the therapeutic agent for combating this infectious disease did not justify his expectation and proved to be the first failure among the many "cures" for the treatment of tuberculosis which were to follow, he established, nevertheless, an important principle of infection which came to be known as the "Koch effect."

Following these two groups of discoveries, a host of investigators, including bacteriologists, protozoologists, mycologists, and virologists, isolated organisms that cause numerous infectious diseases that afflict man and his domesticated plants and animals, established the mode of transmissions of such diseases, and discovered means of prophylaxis and therapy.

It was the search for chemical substances or drugs which could be used in the treatment of infectious diseases that led to another great discovery in the field. Paul Ehrlich, noted for his contribution to immunology, is credited with being the "father of chemotherapy." He not only established the great potentialities of certain dyes and arsenical agents in combating a variety of diseases, such as syphilis, but he pointed to the great potentialities of synthetic chemistry in opening a way for the final control of human diseases. The work of Ehrlich was opposed by a few, but it was readily accepted by chemists and microbiologists, and served to arouse the medical world to the belief that before very long new drugs would be found that would act in a similar manner upon bacterial and other diseases.

Although bitter disappointment soon followed, Ehrlich's prophesy was fulfilled a quarter of a century later with the discovery of the sulfa drugs. The introduction of these compounds ushered in a new era in chemotherapy. It was now established beyond question that not only protozoan and spirochetal diseases, which were successfully treated with arsenical compounds, but bacterial infections as well could be effectively combated by generalized treatment with chemical drugs. Thus the basis was laid for bacterial chemotherapy.

In rapid succession, one drug followed another. Each proved to have certain advantages over the previous ones. New types of compounds were soon added, like the sulfones, which were believed to be able to do for tuberculosis what the others did for most of the bacterial infections.

But there appeared to be a certain limit beyond which these compounds could not reach. There still remained a great many diseases which did not respond to the sulfa drugs, including many caused by Gram-positive and Gram-negative bacteria; the various forms of tuberculosis did not respond well to the sulfones; the virus diseases were not affected at all. Furthermore, these compounds were found to produce frequent toxic reactions and gave rise, under certain conditions, to drug-resistant strains of bacteria.

Fortunately, even before the limitations of the synthetic compounds were fully recognized, a dramatic advance was made in chemotherapy through the microbiological research that led to the discovery of antibiotics. Several major groups of microorganisms, comprising certain bacteria, molds or fungi, and actinomycetes, were found capable of producing various metabolic products which had the capacity of inhibiting the growth of and even of destroying disease-producing bacteria, not only in the test tube but also in the human and animal body. This fundamental principle was first recognized in 1939-1940. It brought about at once a change in the whole problem of chemotherapy. Medical science was revolutionized. Diseases never before believed to be susceptible to therapy were treated with remarkable effectiveness. Old drugs were replaced by new ones, which were more effective and less toxic. Even such apparently resistant diseases as brucellosis and tuberculosis became subject to therapy. One of the most important chapters in the history of science and medicine was written before our eyes.

The discovery of antibiotics served to encourage, rather than discourage, chemical synthesis. New compounds are being tested daily. I need hardly dwell upon some of the substances developed during the war for the treatment of malaria and various animal parasites. The discovery of the effectiveness of isonicotinic acid in the treatment of tuberculosis serves as further evidence of the great potentialities in this field and of the great future for chemotherapy.

The continued search for new antibiotics and the chemical synthesis of new compounds are now proceeding hand in hand, toward the ever-expanding battle against infectious diseases and toward the final triumph of the human mind.

Since the early days of microbiology, the phenomenon known as antagonism or antibiosis has been observed by the student of mixed populations, in soil or in water basins, in mixed infections, and even by the casual observer of contaminated plate cultures of microorganisms. Although the ability of various bacteria and fungi to produce antimicrobial substance has thus long been appreciated, recognition of the great chemotherapeutic potentialities of these substances, now designated as "antibiotics," is of very recent origin. Hardly a dozen years ago, these substances were spoken of as lysins, toxins, bacteriolysins, bacteriotoxins, bacteriostatic, bactericidal and bacteriolytic substances, antibacterial or antagonistic agents, lethal and staling principles, and by a variety of other designations.

It is sufficient to cite in this connection the concepts of Dubos in 1939, who has made a highly im-

portant contribution to the development of this subject. Having succeeded in isolating from the soil an organism which could decompose soluble polysaccharides extracted from certain bacterial pathogens, he proceeded to develop methods for the isolation of microorganisms capable of attacking not only specific cell components, but also the intact living cell itself. This work resulted in the isolation, in 1939, of a bacterial culture which produced a soluble agent that had the capacity to attack and cause lysis of living cells of susceptible Gram-positive bacteria. He spoke of it as "a bactericidal agent extracted from a soil bacillus."

These concepts illustrate the prevailing attitude toward the phenomenon of antagonisms and the production of antibiotics. With certain few exceptions, the chemotherapeutic significance of these compounds was hardly appreciated. Practical applications were thought to be limited. They were looked upon largely as microbiological curiosities.

The mechanisms responsible for the antagonistic properties of microorganisms were not sufficiently understood. Numerous theories were proposed to explain the reactions involved. They included competition for nutrients, competition for space, exhaustion of certain elements in media, physicochemical effects, and production of specific growth-inhibiting substances. There was a special appeal in the concept of "struggle for existence," which was hardly justified on closer examination.

This confusion contributed to a lack of recognition of the potential value of the antibiotic substance in human and animal therapy. When Alexander Fleming described penicillin in 1929, he thought in terms of obtaining cultures of Gram-negative bacteria free from Gram-positive forms. Although he fully appreciated the great therapeutic potentialities of this type of substance, no further investigation of this problem followed for nearly a decade. It was for this reason that neither Raistrick, who attempted to isolate penicillin in 1932, nor Reid, who tried to repeat Fleming's experiments in 1935 in this country, was successful in unravelling this problem.

This was true also of the various investigations of the antibacterial substances produced by different bacteria. It is sufficient to list the numerous studies on pyocyanase, produced by *Pseudomonas aeruginosa*, and the products of *Bacillus subtilis*, *B. mycoides*, and other spore-forming bacteria. Even less can be said of the substances produced by actinomycetes, of which only two enzyme-like preparations were recognized before 1940, in spite of the fact that many of these organisms were known to exert a pronounced growth-inhibiting effect upon various bacteria and fungi. As late as 1938, none of the substances of microbial origin, with the possible exception of pyocyanase, received any consideration as agents with therapeutic potentialities heralding a new era in medicine.

Our modern knowledge of the production and utilization of antibiotics dates back only to the last 13 or 14 years. The isolation of the tyrothricin complex from a spore-forming soil bacterium in 1939, soon followed by the re-isolation of penicillin from fungi in 1941, and by the isolation of actinomycin in 1940 and of streptothricin in 1942 from cultures of actinomycetes, pointed to the great potentialities of microorganisms as producers of antibiotics.

These contributions opened a new chapter in microbiology and especially in human and animal therapy. In this brief span of time, large numbers of well-defined chemical substances now designated as antibiotics have been isolated and tested for their antimicrobial properties. The actinomycetes alone have yielded nearly 100 compounds or preparations. Hundreds of thousands of cultures were isolated from soils, water basins, composts, and other natural substrates. They were examined for their ability to inhibit the growth of pathogenic and saprophytic bacteria, fungi, viruses, protozoa, and insects. Many have been studied further for their capacity to produce antibiotics. Numerous books have been written on the subject. Special journals in various countries and in different languages are devoted to it. Penicillin, streptomycin, bacitracin, chloramphenicol, polymyxin, aureomycin, terramycin, neomycin, and erythromycin have taken an important place in the treatment of numerous infectious diseases caused largely by bacteria, spirochetes, rickettsiae, and some of the larger viruses. Several other compounds are known to be promising therapeutic agents.

Antibiotics are produced by microorganisms and are not to be confused with plant products, such as quinine, and with certain animal products, such as lysozyme, that may possess similar properties. Neither are they to be confused with various organic acids and alcohols that are produced by microorganisms and that are active only in high concentrations.

The formation of antibiotics is limited to certain species and frequently to certain strains of organisms. On the one hand, penicillin is produced by a number of strains of a great variety of fungi belonging largely to the genera *Penicillium* and *Aspergillus*. Streptomycin is produced only by certain strains of *Streptomyces griseus* and of certain other species of *Streptomyces*. Some of these are able to form chemical modifications of this antibiotic, as in the case of hydroxystreptomycin produced by *S. griseocarneus*, or they may give rise to quantitatively different mixtures of the antibiotics, as streptomycin vs. mannosido-streptomycin. Other strains of *S. gri-*

seus may form other antibiotics, such as streptocin and candicidin.

By proper strain selection and by changing the composition of the medium it is possible to increase greatly the yield of the antibiotic and frequently to induce certain chemical variations in its molecular structure as in the case of the different penicillins.

In searching for new antibiotics, it is advisable to consider certain fundamental principles which they should possess before they can qualify as suitable chemotherapeutic agents:

1. They should be selective in their action against bacteria and other microorganisms, and not act as general antiseptics or disinfectants.

2. They should be effective against those microorganisms that are not now subject to the action of antibiotics, or they should be more effective or less toxic than the agents already known.

3. They should exert their antimicrobial activity in the presence of body fluids, and should not be inhibited by substances present in the blood or be destroyed by tissue enzymes.

4. They should be well tolerated when injected into animals in amounts required for combating infections.

5. In concentrations necessary to affect the infectious agent, they should not damage the leukocytes in the blood or be injurious to body tissues.

6. They should be excreted readily, but not too rapidly, from the animal body, and should not accumulate to produce undesirable after-effects.

7. They should not favor the rapid development of resistance among sensitive organisms.

The potential synergistic properties of a new antibiotic with another antibiotic or with a synthetic compound must not be overlooked, even though the new agent may not in itself play an important role in chemotherapy.

The various antibiotics so far isolated and recognized can be classified on the basis of their chemical composition, their antimicrobial spectra, their toxicity to animals, or their chemotherapeutic potentialities.

Chemically, antibiotics range from fairly simple to highly complex compounds. Some contain only carbon, hydrogen, and oxygen. Others are more complex and contain nitrogen (streptomycin—$C_{21}H_{37}O_{12}N_7$), or nitrogen and sulfur (penicillin—$C_9H_{11}O_4SN_2.R$), or nitrogen and chlorine (chloramphenicol—$C_{11}H_{12}O_5N_2Cl_2$). Some are polypeptides (gramicidin, subtilin, and bacitracin), proteins (colicins), or benzene ring compounds. Only very few antibiotics have so far been synthesized, notably penicillin, clavacin, and chloramphenicol; of these, only chloramphenicol has found practical application in therapy. Some of the antibiotics represent single chemical entities, whereas others are made up of several closely related compounds. The latter is true for the penicillins, the streptothricins, the streptomycins, and the aureomycin-terramycin complex. The individual antibiotic entities may vary in their antimicrobial spectra, in toxicity to animals, in stability, and in activity *in vivo*.

Antibiotics also vary greatly in their antimicrobial spectra. Some are active upon a great variety of bacteria, and even upon fungi, rickettsiae, and other groups of microorganisms. Others have very narrow spectra, and are active only upon certain groups of organisms, such as mycobacteria, yeast-like fungi, or certain viruses. Clavacin has a very wide spectrum; penicillin and streptomycin have narrower spectra. Chloramphenicol, aureomycin, terramycin, and erythromycin are active against various bacteria as well as against rickettsiae and some of the larger viruses. Viomycin, esperin, and nocardin are active only upon the mycobacteria; the polymyxins are active largely upon Gram-negative bacteria. Actidione, fradicin, fungicidin, antimycin, ascosin and candicidin are active only upon fungi, with considerable variation in their spectra.

Antibiotics also vary greatly in their toxicity to animals: penicillin is least toxic; actinomycin, streptolin, and xanthimycin are among the most toxic. Clinically, antibiotics vary from important chemotherapeutic agents that are used in the treatment of a great variety of infections, to certain compounds, like tyrothricin, bacitracin, and polymyxin, which have only limited applications.

The microorganisms which are capable of forming antibiotics frequently represent large and variable groups. This is true of the numerous members of the *Penicillium notatum-P. chrysogenum* group, which yield various penicillins; the *Streptomyces griseus* group, which produce the streptomycins; the *S. lavendulae* group, which form streptothricin and a variety of other substances; the *S. aureofaciens-S. rimosus* group, which produce aureomycin and terramycin; and the *B. subtilis* group, which is responsible for more than a dozen compounds possessing antimicrobial properties. There are certain pronounced differences between the various members of these groups of microorganisms. The numerous strains of *Penicillium* vary not only in their quantitative production of penicillin, but also in the nature of the particular type of penicillin.

The fungi have so far yielded one antibiotic that has found practical application, that is, penicillin. The bacteria, notably the spore-forming organisms, have contributed several important agents, mostly polypeptides, some of which, such as tyrothricin, bacitracin, and polymyxin, have found certain applications in therapy. The non-spore-forming bacte-

ria have contributed several antibiotics, of which pyocyanase formerly received much consideration. More recently nisin, a product by a micrococcus, showed at first much promise for the treatment of tuberculosis; this has not been confirmed. The colicins have also received much consideration. The most important antibiotics discovered since penicillin have been obtained largely from cultures of actinomycetes, all from members of the genus *Streptomyces*. These include not only the antibacterial and antifungal agents already listed, but also various antiviral and possibly antitumor agents, which one can only hope may prove to be effective.

Some antibiotics are acids, others are bases, still others are amphoteric compounds. Some are readily soluble in water, others are soluble in organic solvents. Some are heat-stable and others are heat-labile. Some have their optima at a basic reaction, others at a neutral or acid reaction. Some are readily adsorbed from the digestive system into the body fluids, others are not. Antibiotics vary, therefore, in their practical utilization for disease control. Some are most effective orally, others parenterally, still others topically. Among the many antibiotics that have so far been isolated, only very few have found practical application. These are, in order of their discovery:

Tyrothricin has a narrow antibiotic spectrum and is active primarily against Gram-positive bacteria and cocci. It tends to exert a hemolytic effect upon the blood, which limits its use to topical applications.

Penicillin is still probably the most important antibiotic or group of antibiotics discovered so far. It has a fairly broad spectrum, although it is active chiefly against Gram-positive bacteria, various cocci, and spirochetes. It is the least toxic of all. It possesses certain limitations, chief among which are lack of activity against many bacteria, a certain degree of sensitization of many individuals, and the gradual development of resistance to it among certain sensitive bacteria.

Streptomycin tends to fill the gap left by penicillin. Although not so potent, on a weight basis, it is highly effective against a variety of diseases not known previously to be subject to any form of therapy. It has found extensive application in the treatment of tuberculosis, as well as of numerous infections caused by Gram-negative bacteria, such as tularemia and brucellosis, and various Gram-positive bacteria, especially those that have become resistant to penicillin. The limitations of streptomycin comprise the potential causation of vestibular disturbances and its effect on the auditory system when used in large doses, and the rapid development of resistance among sensitive bacteria after prolonged contact with it. Streptomycin and penicillin form an ideal combination for the treatment of numerous diseases.

Chloramphenicol, aureomycin, and *terramycin* are active upon various Gram-positive and Gram-negative bacteria, as well as upon rickettsiae and some of the larger viruses. They are usually administered orally and have found extensive application in the treatment of such diseases as typhoid fever, typhus fever, whooping cough, and trachoma.

Among the other antibiotics that have become established as chemotherapeutic agents, it is sufficient to mention *bacitracin, neomycin,* and *polymyxin*. These compounds tend to exert a somewhat toxic effect when administered parenterally. The first and last also possess narrow spectra. They are, therefore, used largely topically and orally; they are useful in cases of generalized infections that are not readily controllable by other forms of therapy. Neomycin is used alone or in combination with other agents for the treatment of various infections, both orally and topically.

UTILIZATION OF ANTIBIOTICS

Antibiotics have so far found several important fields of application, which can be briefly summarized as follows:

1. Control of numerous infectious diseases of man.
2. Control of diseases of domestic animals.
3. In the nutrition of non-ruminant animals.
4. In the preservation of biological materials, such as bull semen and virus preparations.
5. In certain plant diseases.

There are other potential uses, not as yet clearly understood or developed, as in seed germination and in plant growth.

It is in the treatment of human diseases that antibiotics have made their greatest contribution. It may be truthfully said that antibiotics have revolutionized medical practice. A brief summary may therefore be justified of the role that antibiotics are now playing in the control of various known human and animal diseases.

1. *Diseases caused by cocci (streptococci, pneumococci, staphylococci, gonococci) and various Gram-positive rod-shaped bacteria, comprising aerobic and anaerobic organisms.* These bacteria are highly sensitive to penicillin, to streptomycin, and to a number of other antibiotics, notably aureomycin, terramycin, neomycin, bacitracin, tyrothricin, and erythromycin. These antibiotics have the capacity to attack in a highly efficient manner all of the infections caused by these bacteria. Organisms that become or are resistant to one antibiotic are sensitive to one or more of the others. Recently, there have

come into popular use combinations of two antibiotics, such as penicillin and streptomycin, bacitracin and neomycin, which are usually more effective than a single agent.

2. *Diseases caused by Gram-negative bacteria* are, for the most part, resistant to penicillin, to bacitracin, and to some of the other antibiotics. They are sensitive to streptomycin, chloramphenicol, aureomycin, neomycin, and terramycin, which have found extensive application in the treatment of infections caused by these bacteria. In some cases, as in whooping cough and typhoid, one antibiotic, such as chloramphenicol, is preferable to others. In other cases, as in tularemia, another is more effective, such as streptomycin. In still other cases, as in urinary tract infections, several substances are effective, and can thus be used almost interchangeably, notably, aureomycin, terramycin and neomycin. Certain antibiotics are particularly effective in the treatment of certain types of infection, as in the use of polymyxin for *Pseudomonas* infections. Utilization of the synergistic action of two substances, such as aureomycin and streptomycin, or of an antibiotic with a synthetic agent, such as streptomycin and sulfadiazine, in the treatment of certain infections, offers considerable promise of exerting a greater effect, and tends to overcome the danger of potential development of resistance among the sensitive organisms.

3. *Diseases caused by acid-fast bacteria.* Because of their peculiar characteristics, these diseases are among the most resistant to chemotherapy. The discovery that streptomycin can be utilized in the treatment of tuberculosis has provided a great stimulus to the search for new antibiotics and synthetic compounds that possess similar properties. It has aroused hope that the control of this highly important group of diseases may at last be within our reach. The fact that, among the antibiotics, streptomycin is not alone in this respect is indicated by the latent potentialities of a number of other antibiotics, notably, neomycin, viomycin, mycomycin, and nisin. The possible development of strains of *M. tuberculosis* resistant to streptomycin has suggested the supplementary use of other agents, such as para-aminosalicylic acid. The recent introduction of isoniazid for the treatment of this group of diseases has presented new problems and aroused greater hope.

The treatment of leprosy has not yet been solved satisfactorily, although some antibiotics have been found to be effective. Indications are that, sooner or later, this ancient disease of man will become subject to chemotherapy.

4. *Spirochetal diseases.* Several antibiotics, notably penicillin and bacitracin, have a remarkable effect upon syphilis and other diseases caused by spirochetes. The utilization of antibiotics in the treatment of these infections has gradually superseded the use of salvarsan and other methods of treatment in vogue before the advent of antibiotics.

5. *Rickettsial diseases.* These diseases, comprising typhus fever, scrub typhus, spotted fever, and a variety of others, are readily subject to therapy by a number of antibiotics. These include chloramphenicol, aureomycin, terramycin, and erythromycin, all of which appear to be able to control virtually this whole group of infections. The choice of the particular drug depends largely upon circumstances.

6. *Fungous diseases.* Various antibiotics are known to possess pronounced fungistatic and fungicidal properties. Unfortunately, most of them are too toxic for general use. This is true of actidione, fradicin, fungicidin, and others. Although none has as yet found application in the generalized treatment of fungous infections, there are indications that some antibiotics, such as fungicidin RAW, rimicidin, ascosin, and candicidin, will soon be found capable of controlling some of these diseases.

7. *Protozoan and other diseases due to animal forms.* No true antibiotic is now known to be significantly effective against diseases caused by the malarial and certain other important protozoan organisms. The ability, however, of various agents to affect amebae, trypanosomes, trichomonads, and other protozoa has been definitely established. Some of these substances have already found practical application in chemotherapy. This is true, for example, of aureomycin, terramycin and fumigallin, which are used successfully against amebic dysentery, although it is claimed that the favorable effect consists largely in killing the bacteria upon which the amebae feed.

8. *Viral diseases.* Some of the larger viruses, notably the psittacosis and lymphogranuloma venereum groups, are susceptible to various antibiotics, such as chloramphenicol, aureomycin, and terramycin. The usefulness of these in such viral infections as trachoma has also been definitely established. Their use in other viral diseases, such as mumps, infectious mononucleosis, influenza, and so-called viral pneumonia, requires further confirmation or elucidation. No antibiotic has so far found practical application in the treatment of diseases caused by the smaller viruses, of which the causative agents of the common cold and of poliomyelitis are most important. Recently reports of the formation of specific antiviral agents against some of the viruses were published. The practical potentialities of these preparations, however, have not been established.

9. *Neoplasms.* Tumor or cancer cells are known to be subject to the action of various microorganisms and their products. It is sufficient to mention the effect of certain bacteria such as *Sporosarcina*

ureae, of trypanosomes such as *Trypanosoma cruzii*, and of fungi belonging to the *Aspergillus fumigatus* order. The effective agents so far isolated have proved to be too toxic for practical use. The evidence obtained suggests, however, that sooner or later, suitable chemotherapeutic agents will be found.

10. *Shock and radiation diseases.* When the human or animal body is subject to shock or to the effect of injurious radiations, it becomes a victim of the otherwise uninjurious intestinal flora and other bacteria inhabiting the human body. In combating the injurious action of such bacteria, certain antibiotics, such as neomycin and aureomycin, may prove to be highly helpful. These phenomena may be of tremendous importance in certain emergencies upon which we need not dwell here.

The story of tuberculosis is that of a continuous battle of mankind against one of its greatest enemies, one that has a particular capacity for attacking its victims at a time of great stress, as in war and in immediate postwar periods. No wonder that this dreadful disease has been called the "Great White Plague"! Less than a decade ago, even after the introduction of the sulfa compounds and penicillin, the medical profession was inclined to the belief that no drug effective against tuberculosis would ever be found. The discovery of streptomycin pointed a way to successful chemotherapy of the disease. It has aroused hope that before very long this scourge of mankind will be brought under complete control. Numerous antibiotics are now known to possess antituberculosis properties. Streptomycin, alone or combined with para-aminosalicylic acid or with isoniazid, is a highly important agent in the treatment of tuberculosis.

Numerous clinical investigators followed the early studies of Hinshaw and Feldman in emphasizing the fact that streptomycin reversed the trend of tuberculosis and that the majority of the patients treated were improved. This antibiotic was found to bring about a rapid fall in temperature and accompanying symptomatic improvement and a regression of pulmonary lesions. It has found a definite place in the treatment of miliary tuberculosis and tuberculous meningitis, tuberculous sinuses and fistulas, of bone and joint tuberculosis, and of various forms of early and pulmonary tuberculosis.

The conclusion was reached that the most significant contribution of antibiotics and synthetic compounds in the treatment of tuberculosis is that they have demonstrated that the chemotherapy of this disease, like that of most other infectious diseases, is possible. In my recent travels through southern and western Europe, I was profoundly impressed by the successful results obtained in the treatment of certain forms of tuberculosis by streptomycin. Recovery rates as high as 50 to 75 per cent in cases of meningeal and miliary tuberculosis were claimed.

As one surveys the broader aspects of the subject of antibiotics; as one realizes that a mere fraction of the microorganisms present in numerous soil types throughout the world, in various water basins, on numerous food products, and on many other substrates have so far been examined for their ability to produce antibiotics; as one visualizes the great variety of chemical compounds which are formed by these organisms and which have the capacity of inhibiting the growth of and even of destroying other microorganisms; as one finds that some of the isolated compounds are not very toxic to animals and possess properties which would render them desirable chemotherapeutic agents—one is inclined to become optimistic and to hope that, before long, all human and animal infections, and possibly plant infections as well, can be combated if not completely eliminated by the utilization of antibiotics.

One may stop, therefore, and analyze the problems in the field of antibiotics that face us at present. We recognize the need for:

1. New antibiotics more active against infectious agents that have become resistant to known antibiotics.

2. New antibiotics capable of exerting a synergistic action, when combined with other known chemical or biological agents, in combating chronic diseases, such as brucellosis, leprosy, and tuberculosis.

3. Antibiotics suitable for combating fungous diseases, filterable viruses, and neoplastic diseases.

4. A better understanding of the mode of action of antibiotics upon various microorganisms, of the mechanism of the development of resistance, and the problem of overcoming it.

5. A better understanding of the role of antibiotics in animal nutrition and the over-all effect upon the human body.

6. Antibiotics to be used in the control of plant diseases.

The search for new antibiotics will continue. New approaches will be found and new screening methods will be developed. Many substances will be discovered which will prove to be better than those now known, or which will act upon diseases not susceptible at present to chemotherapy. Finally, more profound knowledge of the physiological and biochemical mechanisms of the action of antibiotics upon bacteria, viruses, and other pathogenic organisms may help to clarify the still obscure aspects of their mode of action, and thus possibly lead to the discovery, or even to the synthesis, of new and better chemotherapeutic agents.

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